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Review

GLS2 (Glutaminase 2)

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Abstract

Mammalian glutaminases are encoded by two paralogous genes, Gls and Gls2, presumably derived by gene duplication of a common ancestor. Each gene codes for two different isoforms. The two transcripts of Gls2, named GAB and LGA, arise through a surrogate promoter usage mechanism. In certain types of malignancies, such as glioblastoma and liver cancers, expression of GLS2 gene is repressed by promoter hypermethylation, which could contribute to the malignant process. The finding that ectopic expression of GLS2 could inhibit proliferation of these tumors led to the hypothesis that this isoenzyme, a transcriptional target of TP53, might play a role as tumor suppressor, in opposition to GLS, regulated by oncogenes and associated to tumorigenesis. However, recent findings indicate that GLS2 is upregulated in some types of cancer (NMYC-amplified neuroblastoma, cervical, colon and lung cancers) and this upregulation paradoxically correlates with poor clinical outcomes.

Keywords
Glutaminase; Neuroblastoma; Cervical cancer; Colon cancer; Lung cancer

Identity

Other names: GA, PAG, GAB, LGA, hLGA
HGNC (Hugo): GLS2
Location: 12q13.3

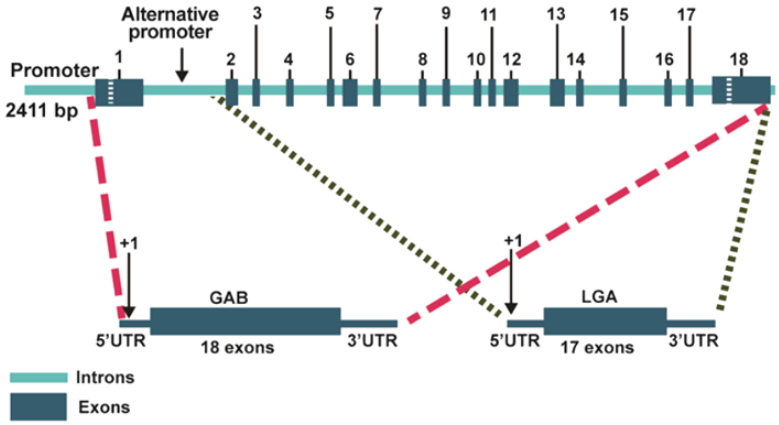

Figure 1. Genomic structure of human glutaminase GLS2 gene and alternative transcripts GAB and LGA. Introns are depicted as solid light blue lines and exons as numbered dark blue boxes. Dashed red or dotted black lines indicate the exons involved in the generation of GAB and LGA transcripts, respectively (Campos-Sandoval et al., 2015).

DNA/RNA

Description

Human GLS2 gene is located on chromosome 12 (Aledo et al., 2000). It is composed of 18 exons and spans approximately 18 kb (Pérez-Gómez et al., 2003). The gene resides on the minus strand. It starts at 56470944 and ends at 56488414 from pter (NCBI, Gene ID 27165).

Transcription

Two GLS2 transcripts coding for functional proteins have been described: a long canonical one containing all 18 exons (GAB), cloned from a human breast cancer cell line (Gómez-Fabre et al., 2000) and a short variant (LGA), first characterized in rat liver (Smith and Watford, 1990; Chung-Bok et al., 1997) and lacking the first exon (Martèn-Rufián et al., 2012). LGA transcript arises by a combination of two mechanisms of transcriptional regulation: alternative transcription initiation and alternative promoter. Its transcription start site is located at 3-end of the first intron of GLS2 gene. Other non-coding transcripts, containing premature stop codons, have been isolated (Martèn-Rufián et al., 2012).

The molecular basis for GLS2 regulation is now starting to be uncovered. GLS2 has been identified as a transcriptional target of tumor suppressor TP53 that mediates its new revealed functions in tumor metabolism and antioxidant defense, under both non-stressed and stressed conditions. This tumor suppressor directly associates with response elements in the GLS2 promoter (Hu et al., 2010; Suzuki et al., 2010). Cells with heightened GLS2 levels showed increased production of glutamate and alpha-ketoglutarate, which resulted in enhanced oxydative phosphorylation, higher GSH/GSSG ratios and decreased reactive oxygen species (ROS) levels, which provided protection against ROS induced apoptosis (Hu et al., 2010; Suzuki et al., 2010). Two other transcription factors belonging to the TP53 family, TP73 and TP63, also drive the expression of GLS2 during neuronal differentiation of neuroblastoma cells after induction with retinoic acid (Velletri et al., 2013) and during epidermal differentiation and in cancer cells exposed to oxidative stress (Giacobbe et al., 2013), respectively. The GLS2 downregulation observed in liver and colon cancer cell lines and in hepatocellular carcinoma has been attributed to its promoter hypermethylation, a mechanism that has been proposed as a marker to identify novel tumor suppressor genes. Chemical demethylation treatment increased the GLS2 mRNA levels in these cells (Zhang et al., 2013; Liu et al., 2014). This mechanism is also responsible for the GLS2 silencing detected in highly malignant glioblastomas, and occurs regardless of their TP53 status (Szeliga et al., 2016). Other factors that regulate GLS2 expression are the MYCN oncoprotein (v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog, encoded by MYCN gene) and the NR5A2 (nuclear receptor subfamily 5 group A member 2), also known as LRH-1 (liver receptor homolog 1). MYCN, an essential MYC family member, directly activates GLS2 transcription in MYCN-amplified neuroblastoma cells. Depletion of MYCN expression by short hairpin RNA caused a pronounced decrease in GLS2 (but not GLS) levels in these cells. Conversely, inhibition of TP53 had no effect on GLS2 induction (Xiao et al., 2015). In hepatoma cells, GLS2 is subjected to direct transcriptional regulation by NR5A2. Silencing of NR5A2 mediated by small interfering RNA reduced GLS2 transcript and protein levels (Xu et al., 2016). Long non-coding RNA (lncRNA) and microRNAs (miRNAs) are also implicated in GLS2 regulation. The lncRNA urothelial carcinoma-associated 1 (UCA1) regulates GLS2 expression levels through interfering with MIR16-1, which binds to the 3'-UTR (untranslated region) of GLS2 mRNA (Li et al., 2016).

Pseudogene

At least one pseudogene has been reported for GLS2 (GenBank: AF110329.1).

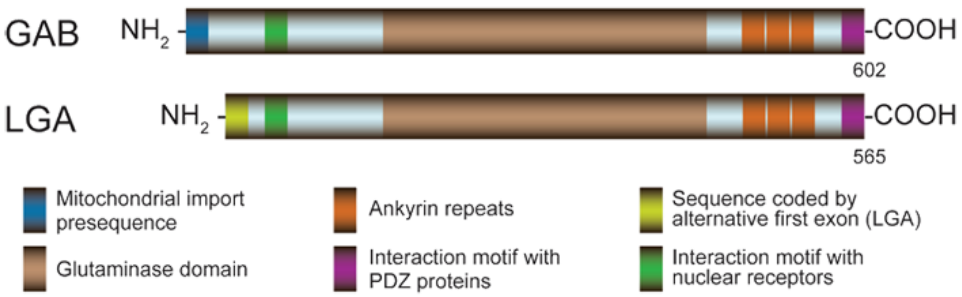

Figure 2. Schematic diagram of GLS2 isoforms showing the localization of predicted domains and motifs by sequence analysis (Márquez et al., 2016).

Protein

Description

Purification: the first attempts to purify liver-type glutaminase from rat liver only yielded partial purifications: 15-fold (Huang and Knox, 1976) and 60-fold (Patel and McGivan, 1984). Unlike kidney-type glutaminase (KGA), the liver isoenzyme does not polymerize in the presence of phosphate-borate buffer (Huang and Knox, 1976). This different behaviour, together with its greater instability in tissue homogenates and diluted preparations, made this isoenzyme more difficult to purify than KGA. In fact, its purification to near homogeneity was not achieved until almost two decades later than KGA purification. Heini et al. (1987) purified rat LGA 400-fold, while Smith and Watford (1988) reported a 600-fold purification, with specific activities of 30-50 μmol/min per mg protein. Human GAB isoenzyme has been expressed as a recombinant protein in baculovirus system and purified by affinity chromatography with a specific activity of 18 μmol/min per mg protein (Campos-Sandoval et al., 2007).

Structure: human GAB transcript (ORF: 1809 nt) codes a 602-residues protein, with a predicted molecular mass of 66.3 kDa. Human LGA transcript (ORF: 1698 nt) codes a 565-residues protein, with a predicted molecular mass of 62.5 kDa. The precursor of human LGA isoform lacks the first 61 residues of GAB precursor (coded by exon 1), but it displays an additional extension of 24 novel residues at the N-terminus coded by an alternative first exon. This extension and the first six amino acids coded by exon 2 are not present in its rat and mouse counterparts (Martèn-Rufián et al., 2012). GLS2 contains a central glutaminase domain of approximately 300 residues, which belongs to the beta lactamase/transpeptidase-like superfamily, and three ankyrin repeats at the C-terminal region (Pasquali et al., 2017). The ankyrin repeats are protein-protein interaction modules of 33 residues that have been found in many important proteins such as transcriptional factors, cell cycle regulators, cytoskeletal organizers, etc. (Sedgwick and Smerdon, 1999; Mosavi et al., 2004). At its C-terminal end there is a consensus sequence of four residues required for specific interaction with PDZ (postsynaptic density protein, disc large, zona occludens) proteins (Olalla et al., 2001). The N-terminal end (first 14 residues) of GAB precursor contains a putative mitochondrial import presequence (Gómez-Fabre et al., 2000). It is worth mentioning the presence of a consensus LXXLL motif of interaction with nuclear receptors at N-terminal region of GLS2 (Olalla et al., 2002). It is in the regions involved with organelle targeting (exon 1) and protein-protein interactions (exon 18) that the main differences between GAB and kydney-type glutaminase reside (Pérez-Gómez et al., 2003). Studies on processing and molecular structure of native GLS2 protein are lacking. An apparent subunit molecular mass of 57-58 kDa for the rat liver isoform was determined by denaturing gel electrophoresis of purified protein (Heini et al., 1987; Smith and Watford, 1988). Sequencing by Edman degradation of the mature form of human GAB expressed in baculovirus system showed cleavage between amino acids 38-39 and 39-40 of the deduced protein sequence. These cleavages are consistent with known substrate sites for the mitochondrial processing peptidase (MPP), having an Arg residue at position -2 or -3. Nevertheless, processing in baculovirus system may somehow differ from the native processing in mammals (Campos-Sandoval et al., 2007). The molecular mass (Mr) of native GLS2 has not been determined accurately. Smith and Watford (1988) reported an Mr of $\geq$ 300000 from HPLC gel filtration but obtained a value of 162000 by sucrose gradient centrifugation, regardless of phosphate concentration (5 or 100 mM).

Kinetic properties: the distinct kinetic behavior of mammalian kydney-type and liver-type isoenzymes was first noted by Krebs (1935). In contrast with kydney-type isoenzyme, the rat liver-type glutaminase showed a lower dependence on the activator inorganic phosphate (Pi), lower affinity for the substrate glutamine, lack of inhibition by glutamate (up to 50 mM) and a requirement for ammonia as an obligatory activator (Verhoeven et al., 1983; Patel and McGivan, 1984; Smith and Watford, 1988). The only human GLS2 protein characterized in a purified form is the recombinant GAB expressed in insect cells. It showed an allosteric behavior (Hill index of 2.7) with low affinity for glutamine ($S_{0.5}$ values of 32 and 64 mM for high (150 mM) and low (5 mM) Pi, respectively), and low dependence for Pi as expected for a GLS2 isoenzyme. Surprisingly, GAB was inhibited by glutamate, a characteristic only shown by GLS isoforms, with an IC_{50} value of 50 mM at low Pi concentrations (5 mM) and suboptimal glutamine concentration (20 mM), and scarcely activated by ammonia (Campos-Sandoval et al., 2007).

Post-translational modifications: several acetylated and succinylated lysine residues have been identified in GLS2 by large-scale proteomic approaches (Rardin et al., 2013; Park et al., 2013).

Expression

The classical pattern of glutaminase expression first established that GLS2 isoforms were restricted to postnatal liver, while GLS isoforms were widely distributed in most nonhepatic tissues (Curthoys and Watford, 1995). Recent findings have extended the range of GLS2 expression to other extrahepatic tissues such as brain, pancreas, cells of immune system and tumor cells (Aledo et al., 2000; Castell et

al., 2004; Gómez-Fabre et al., 2000; Pérez-Gómez et al., 2005). Experimental evidences now support that both glutaminase genes are coexpressed in some tissues as well as in many cell types. Thus, GLS2 co-localized with KGA in numerous cells throughout the brain (Olalla et al., 2002; Cardona et al., 2015). Both GLS2 and GLS transcripts were also found to be co-expressed in liver and brain of rat, mouse and human (Martèn-Rufián et al., 2012). Simultaneous expression of GLS and GLS2 isoforms were also confirmed for several human cancer cells at the transcriptome and proteome levels (Turner and McGivan, 2003; Pérez-Gómez et al., 2005). In different types of cancer, such as bladder, colon and lung cancer, GLS2 is considerably overexpressed compared with normal tissues (Saha et al., 2019).

Localisation

Although glutaminase has long been considered predominantly a mitochondrial enzyme (Curthoys and Watford, 1995), a differential localization for glutaminase was found in neurons using isoform-specific antibodies (Campos et al., 2003): while KGA was present in mitochondria, a Gls2-encoded isoform - most probably GAB - was found in nuclei where it was catalytically active (Olalla et al., 2002).

Function

GLS2 (E.C. 3.5.1.2.) catalyzes the hydrolytic deamidation of L-glutamine to form L-glutamate and ammonium, the first step of glutaminolysis. In liver, GLS2 reaction provides substrates for gluconeogenesis and urea synthesis (Watford, 1993). A role of GLS2 in neuronal differentiation has been recently reported (Velletri et al., 2013). In some cancer cells, GLS2 may play a role as tumor suppressor, in opposition to GLS, regulated by oncogenes and associated to tumorigenesis. GLS2 overexpression in glioblastoma cell lines caused a reversion of their transformed phenotype (Szeliga et al., 2009). This is in agreement with the loss of GLS2 expression in hepatocellular carcinomas (Suzuki et al., 2010) and brain tumors (Szeliga et al., 2005). However, this behavior of GLS2 is not universal, as there are some types of cancer - cervical and lung cancers, NMYC-amplified neuroblastoma - where GLS2 expression is upregulated and this upregulation is associated with therapeutic resistance and poor clinical outcomes (Xiang et al., 2013; Xiang et al., 2015; Saha et al., 2019).

Interacting partners: the first protein-interacting partners of GLS2 were discovered by two-hybrid genetic screening of a human brain cDNA library, using the C-terminal region of GLS2 as bait. Two PDZ domain-containing proteins were isolated: SNTA1 (alpha 1-syntrophin) and TAX1BP3 (Tax1-binding protein 3, also known as Tax-interacting protein 1 (TIP-1) or glutaminase-interacting protein (GIP)). The C-terminal end of human GLS2, -ESMV, matches the consensus sequence X-Ser/Thr-X-Val required for interaction with PDZ proteins (Olalla et al., 2001). A dissociation constant of 1.66 μM was determined for the GLS2-GIP binding, which indicates a moderate affinity suitable for regulatory functions (Banerjee et al., 2008).

Two recent findings have revealed the important role that GLS2 plays in tumor suppression through its interactions with other proteins in a glutaminase activity independent manner. GLS2 binds through its C-terminal region to RAC1 (Rac family small GTPase 1), a critical promoter of metastasis frequently activated in several types of cancer, and inhibits its activation by guanine-nucleotide exchange factors (GEFs). Thus, as a direct target of TP53, GLS2 mediates TP 53's function in metastasis suppression (Zhang et al., 2016). GLS2 also binds to and stabilizes DICER1, a key component of the microRNAs processing machinery, promoting MIR34A maturation. Upregulation of this miRNA represses metastasis in hepatoma cells through expression inhibition of SNAI1 (snail family transcriptional repressor 1), a transcriptional repressor of cadherin 1 (CDH1, also known as E-cadherin) (Kuo et al., 2016).

Implicated in

Drug inhibitors: in contrast to GLS, little effort has been devoted to the search for specific GLS2 inhibitors. In a recent study, Lee and coworkers have described several alkyl benzoquinones isolated from Ardisia virens or Ardisia kusukuensis that selectively inhibit GAB over GLS and display antitumor activity (Lee et al., 2014).

Bladder cancer

GLS2 is overexpressed in bladder cancer (Li et al., 2015; Saha et al., 2019). Urothelial carcinoma-associated 1 (UCA1) is a lncRNA which has been linked to bladder cancer progression and resistance to drugs. Expression levels of UCA1 and GLS2 positively correlated in these tumor cells. UCA1 possesses a binding site for miRNA-16, a repressor of GLS2 expression.

Overexpression of UCA1 resulted in enhanced GLS2 mRNA and protein levels and decreased levels of miRNA-16. Thus, UCA1 reduced ROS generation by acting as a natural molecular sponge to block the tumor suppressor function of miR-16 (Li et al., 2015).

Cervical Carcinoma

Expression of GLS2 is significantly elevated in cervical carcinoma of radioresistant patients compared with that in radiosensitive patients. Silencing of GLS2 expression in radioresistant cancer cells caused downregulation of GSH, NADH and NADPH levels, leading to enhanced levels of

ROS and sensitivity to ionizing radiation (Xiang et al., 2013).

Glioblastoma

GLS2 expression is downregulated in highly malignant glioblastoma (Szeliga et al., 2005; Szeliga et al., 2009). One of the mechanisms involved in this gene silencing was recently demonstrated to be promoter methylation and not related to the TP53 status (Szeliga et al., 2016). Human glioblastoma T98G cells stably transfected with the full GAB cDNA coding sequence showed a reversion of their malignant phenotype, including a marked inhibition in growth and proliferation (Szeliga et al., 2009), downregulation of the expression of DNA-repair gene MGMT and sensitization to alkylating agents (Szeliga et al., 2012). ROS generation by treatment with oxidizing agents synergized with GAB overexpression in T98G glioma cells to suppress their malignant properties, including the reduction of cellular mobility (Martèn-Rufián et al., 2014). This increased sensitivity of GAB-transfected cells to oxidative stress is related to the inhibition of PI3K/AKT pathway (Majewska et al., 2019).

Hepatocellular Carcinoma

GLS2 has been identified as a target of TP53 tumor suppressor gene (Hu et al., 2010; Suzuki et al., 2010) and is frequently downregulated or repressed in some types of cancer, like human hepatocellular carcinoma (Yuneva et al., 2012). It is remarkable that GLS2 transcripts were almost absent or significantly decreased in hepatocellular carcinomas compared to normal liver tissue, where GLS2 is abundantly expressed (Suzuki et al., 2010). A switch from GLS2 to GLS expression was detected in HCC samples compared with surrounding nontumor liver tissue (Xiang et al., 2015). GLS2 downregulation was correlated to its promoter hypermethylation. Ectopic expression of GLS2 led to cancer cell growth inhibition and cell cycle arrest (Zhang et al., 2013). The negative regulation that GLS2 exerts on the PI3K/AKT signaling contributes greatly to its tumor suppressive activity in HCC (Liu et al., 2014). GLS2 also mediates TP53 function in metastasis suppression in HCC through directly inhibiting RAC1, which is central to processes involved in malignant transformation (Zhang et al., 2016), and stabilizing DICER1, which represses SNAIL, a transcriptional repressor of cadherin 1, through miR-34a upregulation (Kuo et al., 2016). Moreover, GLS2 has been proposed, together with DUOX1 (dual oxidase 1) and FBP1 (fructose-bisphosphatase 1), as prognostic markers for HCC patients' survival (Chen et al., 2016).

Colon cancer

As in HCC; Zhang and coworkers reported the downregulation of GLS2 expression in human colon cancer cell lines via promoter hypermethylation. Demethylation treatment increased GLS2 mRNA levels. In addition, ectopic overexpression of GLS2 induced cell cycle arrest at G2/M phase through negative regulation of the CDC25C (cell division cycle 25C) protein phosphatase by phosphorylation on Ser 216. Reduced GLS2 mRNA levels were also observed in 5 cancerous samples from patients with colon cancer (Zhang et al., 2013). Nevertheless, other authors have reported a considerable overexpression of GLS2 in colon cancer samples with respect to normal tissue using expression data extracted from several databases (Giacobbe et al., 2013; Saha et al., 2019).

Lung cancer

Inhibition of GLS2 by a series of alkyl benzoquinones or RNA silencing significantly reduced proliferation of lung cancer cell lines (Lee et al., 2014).

Neuroblastoma

In MYCN-amplified neuroblastomas, GLS2 expression is significantly elevated, correlating with poor prognosis. MYCN directly activates GLS2 but not GLS expression. A Myc response element is found within the first intron of GLS2 gene. Knockdown of GLS2 expression caused glutamine-dependent anaplerosis inhibition, decreased aerobic glycolysis due to thioredoxin-interacting protein (TXNIP) activation, and lowered GSH levels, resulting in proliferation inhibition of these tumors both in vitro and in vivo (Xiao et al., 2015).

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